REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 1-4, 9-11, 14-18, 20-44, and 89-91 are pending. Claims 1-3, 9-10, 17, 18, 21, 24, 26-28, 32-33 and 36-44 have been amended. Claims 5-8, 12-13, 19, and 45-88 have been cancelled. Claims 89-91 are new. The amendments contained herein do not introduce new matter or raise new issues that would require further consideration and/or search.

II. The Invention

In cell NMR spectroscopy provides a new tool for the characterization of macromolecules in their natural intracellular environment. This characterization is achieved through the labeling of selected macromolecules in a cell/biological compartment with a NMR-detectable nucleus such that the NMR-detectable nucleus is present in the selected macromolecule in an amount greater than is naturally abundant. Contacting the biological compartments with radio frequency energy, and then collecting and analyzing the data produced provides structural, conformational and dynamic information for labeled macromolecules within the cell. For example, the methods of the present invention can distinguish individual macromolecules, macromolecule conformations, and interactions of macromolecules with other species within an intact, living cell. In order to optimize the sensitivity of the NMR measurements of the invention, different expression and labeling schemes are used, such as employing the polymerase inhibitor rifampicin to lower background signals, and expressing the intact, living cells in label-rich media.

III. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted.

Many of the claim amendments have been made to clarify sources of antecedent support already existing in the claims. The term "intact" is added to the term "biological compartment" in claims 2, 3, 10, 17, 18, 21, 24, 26, 27, 28, 32, 33, and 38 to clarify antecedent support from "intact biological compartment" found in claim 1. In claim 1, line 3, the term

"NMR-detectable" is added to the term "nucleus" to clarify antecedent support from "NMR-detectable nucleus" found earlier in line 3. In claim 1, line 4, the term "selected" is added to "macromolecule" to clarify antecedent support from "selected macromolecule" found in claim 1, line 2. In claim 9, the term "selected" is added to "macromolecule" in line 1 to clarify antecedent support from "selected macromolecule" found in claim 1, line 3. In claim 17, the term "labeled" is removed from "labeled biological compartment" to clarify antecedent support from "intact biological compartment" found in claim 1, line 2. For the sake of this application, Applicant acknowledges that a "labeled biological compartment" is an intact biological compartment which contains a macromolecule labeled with an NMR-detectable nucleus. In claim 18, the term "of said intact" is added to "unlabeled precursor biological compartment" in order to clarify antecedent support from "unlabeled precursor of said intact biological compartment" in claim 17. In claim 24, the term "unlabeled precursor of said intact" is added to "biological compartment" in order to clarify antecedent support from "unlabeled precursor of said intact biological compartment" in claim 17. In claim 36, the term "using an HNCA experiment" is deleted and the term "wherein said multidimensional multinuclear method is an HNCA experiment" is added to clarify antecedent support from "multidimensional multinuclear method" in claim 35. In claim 37, the term "using an HMQC experiment" is deleted and the term "wherein said multidimensional multinuclear method is an HMQC experiment" is added to clarify antecedent support from "multidimensional multinuclear method" in claim 35. In claim 38, the term "biological" is added to "compartment" to clarify antecedent support from "intact biological compartment" in claim 1. In claim 39, the term "biological" is added to "cell" to clarify antecedent support from "biological cell" in claim 38. In claim 40, the term "prokaryotic" is added to "cell" to clarify antecedent support from "prokaryotic cell" in claim 39. In claim 41, the term "biological" is added to "cell" to clarify antecedent support from "biological cell" in claim 38. In claims 42 and 43, the term "eukaryotic" is added to "cell" to clarify antecedent support from "eukaryotic cell" in claim 41. In claim 44, the term "mammalian" is added to "cell" to clarify antecedent support from "mammalian cell" in claim 43.

Claim 1 is amended at lines 10 and 11 to address the Examiner's 35 U.S.C. § 112, second paragraph rejection of this claim (see Section VI for an explanation of the rejection). Support for this amendment is found in claim 1, lines 1-2 and 11.

Claim 26 is amended to address the Examiner's 35 U.S.C. § 112, second paragraph rejection of this claim (see Section VI for an explanation of the rejection). Support for this amendment is found on page 4, lines 18-21 and page 13, lines 5-12.

New claim 89 is added to further elucidate the structural information provided by the invention. Support for this new claim is found on page 9, lines 30-34, as well as Examples 3 and 5-7.

New claim 90 adds the limitation that the biological compartment is not immobilized during the practice of the invention. Support for this new claim is found on page 9, lines 19-21 and page 23, lines 15-19.

New claim 91 is claim 1 rewritten to avoid the "greater than" language which formed part of the basis for a 35 U.S.C. § 112, second paragraph rejection for claim 1. Support for this new claim is found in claim 1.

Applicant respectfully requests the Examiner's consideration of this matter.

Finally, no new matter is introduced with these amendments.

IV. Response to Restriction Requirement

In a Restriction Requirement on September 30, 2002, the Examiner divided the claims into two groups. Applicant elected Group I with traverse for prosecution. Applicant confirms the earlier election and cancels claims 45-88 as being drawn to a non-elected invention.

V. Response to Defective Oath/Declaration

The Oath/Declaration is rejected as allegedly not being in compliance with 37 CFR § 1.67(a). The Examiner has cited the oath/declaration as defective for not stating that the named inventor is the original, first, and sole inventor, for not identifying the mailing or post

office address of the inventor, and for not identifying the city and either state or foreign country of residence of the inventor. Applicant respectfully traverses.

The Examiner has stated that the oath/declaration is defective for not stating that the named inventor is the original, first, and sole inventor. As Applicant filed a nonprovisional application under 37 CFR § 1.51(b), the oath or declaration must comply 37 CFR § 1.63 or 37 CFR § 1.68. Applicant filed according to 37 CFR § 1.63, which reads in part:

> (a) An oath or declaration filed under § 1.51(b)(2) as a part of a nonprovisional application must:
> . . .(4) State that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.
>
> [37 CFR § 1.63(a)(4)]

As there is no requirement in the Code of Federal Regulations that the inventor must declare him/herself to be the sole inventor, Applicant does not believe that the oath/declaration is defective.

The Examiner has also cited the oath/declaration as defective for not identifying the mailing or post office address of the inventor, and for not identifying the city and either state or foreign country of residence of the inventor. Again, 37 CFR § 1.63 which reads in part:

> (c) **Unless such information is supplied on an application data sheet in accordance with § 1.76,** the oath or declaration must also identify:
>
> > (1) The mailing address, and the residence if an inventor lives at a location which is different from where the inventor customarily receives mail, of each inventor;
>
> [37 CFR § 1.63(c)(1)] [emphasis added]

The Code of Federal Regulations allows an oath/declaration to lack identification of the mailing address, city and state/foreign country of the inventor if this information is provided in an

application data sheet (ADS). Applicant provided this information in an ADS filed with this application; a copy of this ADS is included with this Amendment (Exhibit A).

As the oath/declaration does not require a 'sole inventor' recitation, and Applicant has provided address and residence information in an ADS, the oath/declaration is not defective. Therefore, Applicant requests withdrawal of the rejection.

VI. Response to Claim Rejections

Under 35 U.S.C. § 112, second paragraph

a) Indefiniteness in Claim 1 preamble

Claim 1 is rejected for alleged vagueness and indefiniteness in the recitation in the preamble of "in an amount greater than is naturally abundant". Applicant believes that claim 1 is neither vague nor indefinite, and respectfully traverses the rejection with the arguments presented below. In the event that the Examiner finds Applicant's arguments to be unpersuasive and upholds the 35 U.S.C. § 112, second paragraph, Applicant proposes new claim 91 as an alternative to claim 1, and respectfully requests that the Examiner enters new claim 91 if claim 1 fails.

While the Examiner has cited the phrase "in an amount greater than is naturally abundant" in the rejection, the phrase, the natural abundance of a NMR-detectable nucleus in a macromolecule, is the core term on which the rejection hinges. The specification teaches that any NMR-detectable nucleus is useful in the present invention (page 10, lines 10-12), with specific examples being ^{1}H, ^{15}N, ^{13}C, ^{19}F, ^{31}P and combinations thereof. The specification also defines the term "macromolecule" as follows:

> A macromolecule is a structured molecule that contains one or more components and has a molecular weight of at least about 1000 daltons. Macromolecules of the present invention include biopolymers; synthetic chemical polymers; and chimeric polymers as defined below.
>
> page 7, lines 11-14,

with specific examples being enzymes, transcription factors, antibodies, carbohydrates, nucleic acids, etc. (page 10, lines 20-32). Since each of the NMR-detectable nuclei has a different natural abundance in each of the macromolecules characterizable by the invention, the term, the natural abundance of a NMR-detectable nucleus in a macromolecule, is a variable term.

A claim may be rendered indefinite by reference to an object that is variable. MPEP § 2173.05(b). There are two main tests for determining whether a variable object is indefinite. One is *Ex parte Brummer*, 12 USPQ2d 1653 (Bd. Pat. App. & Inter. 1989) ("*Brummer*"), while the other is *Orthokinetics, Inc. vs. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986) ("*Orthokinetics*"). In *Brummer*, the Board held that a claim limitation to a bicycle that recited "said front and rear wheels so spaced as to give a wheelbase that is between 58 percent and 75 percent of the height of the rider that the bicycle was designed for" was indefinite. While this claim limitation was applicable to many different types of wheelbase: rider height ratios, the Court based its finding of indefiniteness on a lack of description of rider height. In *Orthokinetics*, a claim limitation specifying that a certain part of a pediatric wheelchair be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" was definite. The Federal Circuit in *Orthokinetics* held that the phrase "so dimensioned" was as accurate as the subject matter (the space between a doorframe and a seat in an automobile) permitted. MPEP § 2173.05(b). The alternative, the Federal Circuit stated, would require a recitation of all possible lengths corresponding to hundreds of different automobiles. When the subject matter is so variable, the Federal Circuit noted that patent law does not require this level of recitation.

Applicant's phrase "greater than is naturally abundant in said macromolecule" is definite. As mentioned above, each of the at least five types of NMR-detectable nuclei will have a different natural abundance in each of the macromolecules characterizable by invention. Requiring the Applicant to recite the natural abundances of NMR-detectable nuclei in each relevant macromolecule would be a great burden. In fact, this burden would be greater than the recitation of the hundreds of automobile dimensions which the Federal Circuit, in *Orthokinetics*,

found to be too burdensome. Therefore, Applicant's phrase "greater than is naturally abundant in said macromolecule" is definite, and Applicant respectfully requests withdrawal of this rejection.

b) Indefiniteness for not reciting acronyms/abbreviations in the claims

Claims 1, 3, 15, 16, 17, 36, and 37 are rejected as allegedly not reciting an acronym or abbreviation (NMR for claims 1, 3, 15, and 17; NMR, HSQC and TROSY for claim 16; HNCA for claim 36; and HMQC for claim 37) at least one time in the set of claims. Applicant respectfully traverses.

The Examiner has stated that an acronym or abbreviation must be fully defined and recited at least one time in a set of claims. However, 37 CFR § 1.75 states, in part:

> The claim or claims must conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that **the meaning of the terms in the claims may be ascertainable by reference to the description.**
>
> [37 CFR § 1.75(d)(1)] (emphasis added)

According to the Code of Federal Regulations, acronyms and abbreviations need not be recited in the claims, so long as the meaning of the acronyms and abbreviations are ascertainable by reference to the description. In light of this, the above-cited acronyms and abbreviations are found in the following sections of Applicant's specification: HSQC (page 11, lines 13-14); TROSY (page 11, lines 30-33); and HMQC (page 11, lines 14-15). Applicant has amended the specification in the following sections to clearly support the following acronyms and abbreviations: NMR (page 1, line 9); and HNCA (page 11, line 26). As these amendments are merely reciting and defining acronyms and abbreviations which already appear in the application, the scope of the specification is not being enlarged by these amendments. In order to verify that the specification scope is not being enlarged, the sources of the specification amendments are submitted as Exhibit B (for NMR, Streitweiser, *et al.*, Introduction to Organic Chemistry, 4th Ed., revised printing, (1998) p. 325) and Exhibit C (for HNCA, "Nomenclature of triple resonance experiments" and "The HNCA Experiment", pages three and four of "Three Dimensional NMR Spectoscopy"; from

http://www.cryst.bbk.ac.uk/PPS2/projects/schirra/html/3dnmr.htm#HNCA; accessed August 26, 2003).

As these claims are no longer indefinite, Applicant respectfully requests withdrawal of the rejection.

c) Indefiniteness in Claim 1, step c)

Claim 1 is rejected as vague and indefinite for not reciting, in step c), "said structural information from the NMR data set". Claim 1 has been amended to recite this phrase. Therefore, Applicant respectfully requests withdrawal of this rejection.

d) Indefiniteness in "small"

Claim 5-8, 12, 13 and 19 are rejected for not defining the term "small" in reference to the size of a molecule. As Applicant has canceled claims 5-8, 12, 13, and 19, the rejection is moot. Applicant therefore respectfully requests withdrawal of the rejection.

e) Indefiniteness in "combinations thereof"

Claim 13 is rejected as vague and indefinite for reciting "combinations thereof". As Applicant has canceled claim 13, the rejection is moot. Applicant therefore respectfully requests withdrawal of the rejection.

f) Lack of antecedent basis in Claim 19

Claim 19 is rejected for lacking antecedent basis in reciting, "NMR sensitive nucleus". As claim 19 has been cancelled, the rejection is moot. Applicant therefore respectfully requests withdrawal of this rejection.

g) Indefiniteness in Claim 26

Claim 26 is rejected for two reasons. One, the term "experiences" is allegedly non-idiomatic and confusing. Two, it is allegedly unclear how the viscosity of macromolecule relates to the structural information. Applicant has amended claim 26 to both remove the term "experiences" and redefine viscosity in terms of the biological compartment. Since the confusing word has been removed and viscosity has been directly defined in terms of the

compartment that contains the viscous material, claim 26 is in condition for allowance. Therefore, Applicant respectfully requests withdrawal of this rejection.

Under 35 U.S.C. § 102

To maintain a *prima facie* case of anticipation, the Examiner must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single enabling prior art reference. The identical invention must be shown in as complete detail as is contained in the ...claim. See MPEP § 2131. Applicant submits that one prior art reference of record (Williams) does not disclose each element of the claims now pending. In addition, Applicant submits that one prior art reference of record (Serber) cannot serve as a 35 U.S.C. § 102(e) prior art reference. Therefore, Applicant respectfully traverses this rejection.

a) Under 35 U.S.C. § 102(b): Over Williams, et al. ("Williams")

Claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44 are rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Williams, *et al.*, *BioPhysical Journal*, **72**: 490-498 (1997). Claims 5 and 13 were also rejected as allegedly being anticipated, but these claims have since been cancelled and therefore the rejection is moot. The Examiner has cited Williams for teaching the extraction of structural or conformational information from a NMR data set for macromolecules using ^{19}F NMR longitudinal relaxation time measurements to assess their rotational mobility in the intact cells. However, the cited reference fails to teach all of the claimed elements of the invention. In particular, Williams does not teach the *in vivo* determination of structural information.

Applicant's invention discloses a method of determining structural information about a macromolecule *in vivo* through the use of multidimensional NMR methods. The data collected from these multidimensional NMR methods can be used to ascertain a ***macromolecule's conformation through determining the relative positions of two of more atoms in the macromolecule***. The Examples in the present application disclose a variety of methods of improving the collection of this structural information, from employing the polymerase inhibitor rifampicin in Example 3 to lower background signals, to improving spectral

quality by expressing cells in label-rich media in Example 6. The results of these, and other, methods of collecting structural information are shown in Figures 1-3 and 5-6.

In contrast to Applicant's invention, Williams does not teach the *in vivo* determination of structural information about a macromolecule. Instead, ***Williams discloses the determination of rotational mobility characteristics of a protein***. Rotational mobility concerns how fast a macromolecule is rotating, or "tumbling", in a cell. Since the rate of "tumbling" of a macromolecule in a cell does not provide structural information about the macromolecule itself, Williams does not teach the element of *in vivo* determination of structural information about a macromolecule found in Applicant's invention.

In addition, Applicant's invention and Williams' invention differ in the type of NMR methods employed. Applicant determined *in vivo* structural information about a macromolecule through the use of multidimensional NMR methods. In contrast, Williams determined rotational mobility data through the use of single-dimensional NMR methods. While single-dimensional NMR methods can ascertain the relative chemical environment of the atoms in a molecule and a molecule's rotational mobility, single dimensional NMR is unable to display macromolecular conformations, or exact bond distances. Since Williams does not utilize a NMR method suitable for determining structural information about a macromolecule, Williams again does not teach the element of *in vivo* determination of structural information about a macromolecule found in Applicant's invention.

Williams does not disclose each and every element of Applicant's invention, as disclosed in claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44. Accordingly, a *prima facie* case of anticipation can not be set forth. Therefore, claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44 are in condition for allowance and Applicant respectfully requests withdrawal of the rejection.

b) Under 35 U.S.C. § 102(e): Over Serber, et al. ("Serber")

Claims 1-4, 10, 11, 15-17, 21, 29, 32, and 38-42 are rejected as allegedly being anticipated under 35 U.S.C. § 102(e) by Serber, *et al.*, *J. Am. Chem. Soc.*, **123**: 2446-2447 (2001). Serber is cited for teaching the use of high-resolution in-cell NMR spectroscopy to

provide conformation information, *i.e.*, three-dimensional structures, in the form of NMR spectra, of macromolecules such as overexpressed proteins, *i.e.*, MerA, inside living bacterial cells.

> For an invention to serve as a 35 U.S.C. § 102(e) reference, it must be:
>
> (1) an **application for patent** . . .by another filed in the United States before the invention by the applicant for patent or
> (2) a **patent** granted on an application for patent by another filed in the United States before the invention by the applicant for patent . . ."
>
> [35 U.S.C. § 102(e)] (emphasis added)

Since Serber is a scientific publication, and not an application for patent or patent as required by 35 U.S.C. § 102(e), Serber cannot serve as a 35 U.S.C. § 102(e) reference. Therefore, Applicant respectfully requests withdrawal of the rejection.

Applicant also respectfully requests the permission of the Examiner to file a declaration according to *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) ("*Katz*" declaration). Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. § 102(a). MPEP § 2132.01. Where the Applicant is one of the co-authors of a publication cited against his or her application, the publication may be overcome by submission of a specific declaration by the Applicant establishing that the article is describing Applicant's own work. MPEP § 2132.01. In the instant case, Serber is a publication cited against Applicant. Serber is also a publication that Applicant co-authored. Since the other co-authors of Serber were working under the supervision of the Applicant, the invention is the product of the Applicant's own work. Therefore, Applicant submits a *Katz* declaration for consideration in this case (Exhibit D).

The *Katz* declaration submitted with this amendment is unsigned. A properly signed *Katz* declaration will be resubmitted soon.

Under 35 U.S.C. § 103(a)

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion

or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). As explained below, the cited references fail to disclose the element of *in vivo* determination of structural features of a macromolecule. Therefore, Applicant respectfully traverses the following rejections.

a) Over Williams

Claims 27 and 28 are rejected as allegedly being obvious over Williams. Williams is described above.

The reference cited by the Examiner fails to teach all of the claimed elements of the invention. In particular, Williams does not teach *in vivo* determination of structural features of a macromolecule.

Applicant's invention discloses a method of determining structural information about a macromolecule *in vivo* through the use of multidimensional NMR methods. The data collected from these multidimensional NMR methods can be used to ascertain a macromolecule's conformation through determining the relative positions of two of more atoms in the macromolecule. The Examples in the application disclose a variety of methods of improving the method of collecting this structural information, from employing the polymerase inhibitor rifampicin in Example 3 to lower background signals, to improving spectral quality by expressing cells in label-rich media in Example 6. The results of these, and other, methods of collecting structural information are shown in Figures 1-3 and 5-6.

In contrast to Applicant's invention, Williams does not teach the *in vivo* determination of structural information about a macromolecule. Instead, ***Williams discloses the determination of rotational mobility characteristics of a protein***. This rotational mobility information is collected through the use of a single dimensional NMR method. While single-dimensional NMR methods can ascertain the relative chemical environment of the atoms in a molecule and a molecule's rotational mobility, single dimensional NMR is unable to display macromolecular conformations, or exact bond distances. Because Williams does not teach a method which can determine macromolecular conformations, Williams does not disclose

Applicant's element of *in vivo* determination of structural features of a macromolecule. Because Williams fails to teach all elements of Applicant's invention, a *prima facie* case of obviousness cannot be set forth.

Therefore, Applicant respectfully requests withdrawal of the rejection.

b) Over Williams, in view of Brown, et al. ("Brown"), and further in view of Fesik, et al. ("Fesik")

Claims 9, 20, and 35-37 are rejected as allegedly being obvious over Williams, in view of Brown (U.S. Patent No. 5,817,474), and further in view of Fesik (U.S. Patent No. 5,989,827). Claims 6-8, 12, and 19 were also rejected as allegedly being obvious, but these claims have since been cancelled and therefore the rejection is moot.

The references cited by the Examiner fail to teach all of the claimed elements of the invention. In particular, none of the cited references disclose the element of *in vivo* determination of structural features of a macromolecule.

Williams is described above. Brown is cited for teaching a method for determining the three-dimensional structure conformation of a protein by growing a mammalian cell culture which produces the protein in a nutrient medium which contains all the essential amino acids for the growth of cells, and wherein the amino acids are substantially isotopically labeled with NMR active isotope. Fesik is cited for teaching a method of identifying a small molecule ligand to the protein using two dimensional $^{15}N/^{1}H$ NMR correlation spectroscopy, then identifying a second small molecule ligand to the protein using two dimensional $^{15}N/^{1}H$ NMR correlation spectroscopy. These references cited by the Examiner fail to teach all of the claimed elements of the invention. In particular, none of the cited references teach the *in vivo* structural determination of a macromolecule.

As mentioned above, Williams does not teach the *in vivo* determination of a structural feature of a macromolecule. Instead, Williams discloses the determination of rotational mobility characteristics of a protein through single dimensional NMR methods. Because Williams does not teach a method which can determine macromolecular conformations,

Williams does not disclose Applicant's element of *in vivo* determination of a structural feature of a macromolecule.

Brown describes the *in vitro* structural determination of a protein using multidimensional NMR. According to the method of Brown, a cell culture capable of producing the protein of interest is grown and the protein is assembled, in part, with NMR-detectable nuclei to create a labeled protein. The labeled protein is then isolated from the cell culture medium and subjected to NMR spectroscopic analysis to determine information about its structural conformation. Because the analyzed, labeled protein in Brown is isolated from cells before it is subjected to NMR analysis, Brown does not teach *in vivo* structural determination. Therefore, Brown does not disclose Applicant's element of *in vivo* determination of a structural feature of a macromolecule.

Finally, Fesik describes the *in vitro* structural determination of a ligand binding to a specific target molecule using multidimensional NMR. According to the method of Fesik, a protein of interest is isolated from a culture medium and purified. Then a two-dimensional NMR spectrum is acquired for the protein. Next, the protein of interest is exposed to a series of test ligands and two-dimensional NMR spectrums of the protein-ligand complexes are collected to determine which complexes have optimal binding properties. Because the analyzed protein in Fesik is isolated from cells before it is subjected to NMR analysis, Fesik does not teach *in vivo* structural determination. Therefore, Fesik does not disclose Applicant's element of *in vivo* determination of a structural feature of a macromolecule.

As the combination of cited references does not disclose the element of *in vivo* structural determination of a macromolecule, a *prima facie* case of obviousness cannot be set forth.

Applicant respectfully requests withdrawal of this obviousness rejection.

c) Over Williams, in view of Adams, et al. ("Adams")

Claims 24 and 25 are rejected as allegedly being obvious over Williams, in view of Adams (U.S. Patent No. 5,378,620). Williams is described above. Adams is cited for disclosing rifampicin as an antibiotic that inhibits RNA polymerase in bacteria, *i.e., E. coli*, that

exhibits LEU-2 expressing plasmid. The references cited by the Examiner fail to teach all of the claimed elements of the invention. In particular, none of the cited references teach the *in vivo* structural determination of a macromolecule.

As mentioned above, Williams does not teach the *in vivo* determination of a structural feature of a macromolecule. Likewise, Adams primarily describes the production of hemolytically active, soluble Streptolysin O derivatives. There is no discussion of Applicant's *in vivo* structural determination element in Adams. As the combination of cited references does not all the elements of Applicant's invention, a *prima facie* case of obviousness cannot be set forth.

Applicant respectfully requests withdrawal of this obviousness rejection.

d) Patentability of new claims 89-91 over the cited references

New claim 89 is patentable over the references cited in this Office Action because none disclose the element of *in vivo* determination of macromolecular conformations, or exact bond distances. Williams discloses a single dimensional NMR method of determining a molecule's rotational mobility. Since single-dimensional NMR methods cannot display macromolecular conformations, Williams is not a citable reference here. Likewise, both Fesik and Brown disclose *in vitro* methods of structural determination, and thus do not suggest an *in vivo* method of structural determination. Finally, Adams does not teach the use of NMR and thus does not suggest an *in vivo* method of NMR structural determination. Therefore, Applicants believe that claim 89 is in condition for allowance.

New claim 90 is patentable over the references cited in this Office Action for two reasons. One, as discussed above, none of the cited references disclose the element of *in vivo* determination of macromolecular conformations. Two, none of the cited references disclose the element of conducting the NMR methods on non-immobilized cells. The imaged cells in Williams are specifically immobilized (see page 491, column 1, second full paragraph). As there is no disclosure in Williams that non-immobilized biological compartment are a viable option for use in the invention, Williams is not a citable reference here. Likewise, Fesik, Brown, and Adams are not citable references, because all three do not employ immobilized biological compartments. Therefore, Applicants believe that claim 90 is in condition for allowance.

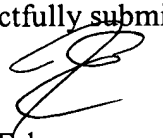
New claim 91 is patentable over the references cited in this Office Action because none disclose the element of *in vivo* determination of macromolecular conformations, or exact bond distances. Williams discloses a single dimensional NMR method of determining a molecule's rotational mobility. Since single-dimensional NMR methods cannot display macromolecular conformations, Williams is not a citable reference here. Likewise, both Fesik and Brown disclose *in vitro* methods of structural determination, and thus do not suggest an *in vivo* method of structural determination. Finally, Adams does not teach the use of NMR and thus does not suggest an *in vivo* method of NMR structural determination. Therefore, Applicants believe that claim 91 is in condition for allowance.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Todd Esker
Reg. No. 46,690

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
TE:te
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